UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
BEAUMONT DIVISION

JUDY ROMERO,	§	
	§	
Plaintiff,	§	Civil Action No. 1:03-CV-01367-MAC
	§	
vs.	§	
	§	
WYETH LLC,	§	Honorable Marcia A. Crone
	§	
Defendant.	§	

WYETH'S MOTION TO EXCLUDE THE TESTIMONY OF ELIZABETH NAFTALIS, M.D. AND JAMES WALDRON, M.D. AND BRIEF IN SUPPORT

Pursuant to Federal Rule of Evidence 702 and *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), Defendant Wyeth LLC f/k/a Wyeth, Inc. and Wyeth Pharmaceuticals, Inc. ("Wyeth") files this Motion to Exclude the Testimony of Elizabeth Naftalis, M.D. and James Waldron, M.D. and Brief in Support, and would respectfully show the Court as follows:

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I. INTRODUCTION

This case arises out of Plaintiff Judy Romero's use of Premphase and Prempro, which are estrogen-plus-progestin ("E+P") hormone therapy medications ("HT"). The Food and Drug Administration ("FDA") approved both of these prescription medicines as safe and effective at the time Ms. Romero took them from 1996-2001, and they are still approved by the FDA as safe and effective today.

Ms. Romero claims that her use of HT caused her breast cancer, which was diagnosed in 2001 as ductal carcinoma in situ ("DCIS") of the left breast.[1] She has designated Dr. Elizabeth Naftalis, a former breast surgeon, and Dr. James Waldron, a pathologist, to testify about specific causation. Both offer scientifically unsound opinions because they purport to use "differential diagnosis" as their methodology, but do not reliably apply such methodology. There is no reliable scientific evidence that HT can cause DCIS, and therefore Drs. Naftalis and Waldron cannot reliably "rule in" HT use as a cause of Ms. Romero's breast cancer. Furthermore, they cannot rule out other recognized causes of Ms. Romero's breast cancer, including the fact that the cause of breast cancer is largely unknown by medical science. Consequently, each should be precluded from offering expert testimony under the principles announced in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993) and its progeny.

II. PLAINTIFF'S EXPERTS AND THEIR OPINIONS

Dr. Elizabeth Naftalis. Plaintiff's main specific causation expert is Dr. Elizabeth Naftalis, a retired breast surgeon who now works for plaintiffs in HT lawsuits. In 2004, Dr. Naftalis left the practice of medicine to be a full-time parent, only recently returning to medicine

[1] DCIS is a non-invasive breast cancer that starts in the milk ducts. It is non-invasive because it has not spread beyond the milk duct into any surrounding breast tissue. *See* **Exhibit 28 –** Oral Deposition of James A. Waldron (June 15, 2011) ("Waldron Dep.") at 25:3-14.

in a part-time capacity; she sees patients at a clinic for one-and-a-half days per month, while spending 80 to 120 hours per month working with plaintiffs' lawyers in HT litigation.[2] She is not a pathologist and does not conduct laboratory tests on breast cancer tissue.[3] She is not a medical oncologist and does not typically treat breast cancer patients.[4] She is also not a cell biologist or an epidemiologist.[5] Dr. Naftalis will opine that but for Ms. Romero's use of HT medications, she would not have developed DCIS of the left breast.[6]

The 43-page report of Dr. Naftalis, dated April 4, 2011, is virtually verbatim to every other report she has submitted in HT litigation across the country. Despite having no training in epidemiology, cell biology, or pathology, almost no research experience, and only a handful of published articles, Dr. Naftalis claims that she has developed a methodology for determining the cause of an individual woman's breast cancer.[7] Her method is deceptively simple. She first presumes that tumors that test positive for the presence of estrogen receptors (i.e., ER+) require estrogen to grow.[8] Second, she assumes that if a woman experienced menopausal symptoms such as hot flashes or heavy and irregular bleeding, she was "hormone deficient."[9] Based on these two data points alone – and without any objective evidence of Ms. Romero's endogenous

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2 **Exhibit 25 –** Declaration and Expert Report of Elizabeth Z. Naftalis, *Romero v. Wyeth LLC* (Apr. 4, 2011) ("Naftalis Report") at 1-2; **Exhibit 1 –** Oral Deposition of Elizabeth Naftalis, M.D. (June 6, 2011), *Briggs v. Wyeth, et al.* ("Naftalis *Briggs* Dep.") at 7:2–10:12; **Exhibit 2 –** Trial Transcript (Oct. 7, 2011), *Curtis v. Wyeth* (E.D. Ark.) at 317:1-319:23.

3 **Exhibit 3 –** Oral Deposition of Elizabeth Z. Naftalis, M.D. (June 18, 2010), *Finn v. Wyeth, et al*. (D. Minn.) ("Naftalis *Finn* Dep.") at 39:2–6; **Exhibit 25 –** Naftalis Report at 37 (relying on findings made by pathologist).

4 **Exhibit 3 –** Naftalis *Finn* Dep. at 139:6-9.

5 *Id.* at 140:2-7; **Exhibit 4 –** Hearing Transcript (Jan. 19, 2010), *Singleton v. Wyeth et al*. (Pa. Ct. Comm. Pleas) ("*Singleton* Hearing Transcript") at 188:8-11.

6 **Exhibit 25 –** Naftalis Report at 41-42.

7 *Id*. at 1-3.

8 *Id*. at 7, 29-30.

9 *Id*. at 10-13.

or native hormone levels[10] – Dr. Naftalis opines that Romero's ingestion of HT must have caused her to develop DCIS in her left breast.[11] Dr. Naftalis posits that HT was the only possible source of hormones that could have fueled a "hormone dependent" carcinoma: "As a hormone deficient woman, no other risk factor would account for any current source of hormones. . . . [A]bsent ingestion of E+P, it is more likely than not that Ms. Romero would not have developed the breast cancer at issue."[12] Thus, on the basis of just three facts – that Romero reported menopausal symptoms, that she took HT, and that she developed an ER+ tumor – Dr. Naftalis concludes that but for HT, Romero would not have developed DCIS.[13]

Dr. Naftalis refers to her methodology as a "differential diagnosis."[14] But that term simply refers to the process that a clinician uses to diagnose a patient's condition; it is not a method to determine what caused the condition in the first place. Although Dr. Naftalis claims to have ruled out all of the other possible causes (known and unknown) of Romero's breast cancer, she did not rule out Romero's age, failure to breastfeed, oral contraceptive use, or her documented breast density, which are all risk factors for breast cancer.[15] Dr. Naftalis even admitted that Ms. Romero's breast density placed her at high risk of breast cancer – four to six times greater than the normal population.[16]

Dr. James Waldron. The proffered opinion of Dr. Waldron, a pathologist, is similarly unreliable. In his three-page report dated March 29, 2011, he also purports to use "differential

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[10] **Exhibit 27 –** Deposition of Elizabeth Z. Naftalis, M.D. (June 24, 2011) ("Naftalis Dep.") at 56:12-19.

[11] **Exhibit 25 –** Naftalis Report at 41-43.

[12] *Id*. at 41.

[13] *Id*.

[14] *Id.* at 8, 29-36.

[15] *Id*. at 30-42.

[16] **Exhibit 27 –** Naftalis Dep. at 34:15-24, 48:12-17, 53:21-54:4.

diagnosis" to opine that Plaintiff would not have developed breast cancer but for her use of combination HT (i.e., E+P).[17] As with Dr. Naftalis's opinion, a differential diagnosis is an insufficient basis for a reliable expert medical causation opinion. Dr. Waldron made no effort to exclude any of Ms. Romero's risk factors for breast cancer at all, and for this additional reason, his testimony fails to meet the *Daubert* criteria.

III. SUMMARY OF THE ARGUMENT

Plaintiff's experts' specific causation opinions are inadmissible and should be excluded on the following grounds:

First, their opinion is based on pure speculation. *See In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717 (3d Cir. 1994); *Moore v. Ashland*, 151 F.3d 269, 276 (5th Cir. 1998) (en banc). Where an expert extrapolates from sparse data to reach his or her conclusion, there is "simply too great an analytical gap" to support admissibility. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Second, Drs. Naftalis and Waldron both purport to use a "differential diagnosis" methodology to reach their conclusions but fail to actually follow that methodology in formulating the proffered opinions. They cannot reliably "rule in" HT use as a cause of Romero's DCIS because there is no scientific evidence that HT can cause DCIS. Furthermore, although they admit that certain risk factors could have been "contributing factors" or may have "played a role" in the development of Romero's DCIS, neither rules out her other risk factors as a cause.[18] This methodological deficiency is fatal to the reliability and admissibility of their opinions. Similar attempts to draw conclusions regarding causation from flawed differential diagnoses have been rejected by the Fifth Circuit. *See Moore*, 151 F.3d 269. Moreover, a well-

[17] **Exhibit 26 –** Report of James Waldron, M.D., Ph.D. (Mar. 29, 2011) at ¶¶ 6, 11.

[18] **Exhibit 25 –** Naftalis Report at 30-42; **Exhibit 26 –** Waldron Report at ¶ 11.

established line of cases from across the country, discussed in section V.A. below, recognize that "differential diagnoses" to determine the cause of a disease are inadmissible when the cause of a disease is to a great extent unknown. The reason is simple: when the cause of a disease is unknown in a significant percentage of cases, a doctor cannot rule out ***all*** causes save one, because even after ruling out all known causes, unknown causes remain. In a consistent line of cases over the last fifteen years, federal courts have ruled differential diagnoses inadmissible in cases involving asthma, autism, brain cancer, leukemia, and other conditions for which the majority of causes remain uncertain. This line of cases represents a specific application of the general principle that when there is too great an analytical gap between the data and the opinion offered, *Daubert* is not satisfied. *See Gen. Elec. Co.*, 522 U.S. at 146; *see also Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 592-93 (1993); *Bland v. Verizon Wireless, L.L.C.*, 538 F.3d 893 (8th Cir. 2008); *Gammill v. Jack Williams Chevrolet, Inc.*, 972 S.W.2d 713, 726 (Tex. 1998).

Third, their opinions are offered only for purposes of litigation. The lack of scientific underpinning for Dr. Naftalis's methodology is apparent from the fact that she always arrives at the same conclusion, no matter the particulars about the individual plaintiff. At a recent deposition in an HT case, she conceded that she has provided the following completely inconsistent opinion testimony. She has opined:

- that HT caused every type of breast cancer – ductal (in the milk ducts), lobular (in the glands of the breast), mixed ductal-lobular, and tubular breast cancer (a rare type of invasive ductal carcinoma);

- that HT caused breast cancer in cases of short-term HT use and in instances of long-term HT use;

- that HT caused breast cancer in cases where the progesterone receptor was negative as well as in cases where the progesterone receptor was positive;

- that HT caused breast cancer where the woman's vasomotor symptoms were severe, where the symptoms were moderate, where the symptoms were mild, and even where the plaintiff reported that she had no symptoms at all;

- that HT caused breast cancer where the plaintiff never drank alcohol, drank only a little, drank moderately, or drank socially;

- that HT caused breast cancer in women who were obese, in women who were morbidly obese, and in women who were not obese at all;

- that HT caused breast cancer in women whose breast density increased while using HT, in women whose breast density stayed the same, and in women whose breast density decreased;

- that HT caused breast cancer in women whose onset of menopause was early and in women whose onset of menopause was late;

- that HT caused breast cancer in women whose first menstruation was early and in women whose first menstruation was late;

- that HT caused breast cancer in women who had no prior breast biopsies, in women with prior benign breast biopsies, and in women with abnormal breast biopsies;

- that HT caused breast cancer in women who had no children, in women who had children early in life, and in women who had children late in life;

- that HT caused breast cancer in women who had breastfed their children and in women who had not breastfed their children;

- that HT caused breast cancer even where the plaintiff had a significant family history of breast cancer; and

- that HT caused breast cancer in women with high Gail Model scores, which indicates an increased risk of breast cancer from factors other than HT.[19]

These admissions demonstrate that Dr. Naftalis predictably renders the same opinion in every case in which she testifies, regardless of a particular woman's background. This shows that her testimony is not scientific, but used only for litigation purposes. The same is true for Dr. Waldron – his report is virtually verbatim with his reports in other HT cases. As discussed in

[19] **Exhibit 5 –** Oral Deposition of Elizabeth Naftalis, M.D., *LaFerrara v. Wyeth, Inc.*, Case No. 4-04-CV-02271 (W.D. Ark.) (May 21, 2010), at 152-60.

more detail below, Plaintiff's specific causation experts should be precluded from offering testimony in this case.

IV. RELEVANT FACTS

A. Background Regarding HT

FDA-approved HT medicines are indicated for the treatment of menopausal symptoms and vaginal atrophy, as well as the prevention of osteoporosis. Since 1942, when Wyeth first introduced HT to the market, until the present day, doctors have prescribed such medicines to menopausal women. At all relevant times, the HT products prescribed to Romero carried warnings that HT use was associated with an increased risk of breast cancer.

In the 1990s, the National Institutes of Health ("NIH") undertook a massive randomized clinical trial – the Women's Health Initiative ("WHI") – to evaluate the risks and benefits of E+P combination HT. The study was one of the largest randomized clinical trials ever done to study the health of post-menopausal women; by several orders of magnitude, it was the largest clinical trial ever involving E+P. The medical and scientific communities, as well as plaintiff experts, defense experts, and the MDL Court in this litigation, recognize WHI as the "gold-standard" and the best data regarding the benefits and risks of HT in post-menopausal women.[20] The MDL

[20] The WHI results were important because the medical community considers clinical trials to be the most reliable form of scientific evidence, and far superior to observational studies. *See* FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 338 (2d ed. 2000); **Exhibit 6 –** STEPHEN B. HULLEY, ET AL., DESIGNING CLINICAL RESEARCH 157–58, 195 (3d ed. 2007); **Exhibit 7 –** Steven Piantadosi et al., *Larger Lessons from the Women's Health Initiative*, 14 EPIDEMIOLOGY 6–7 (2003); **Exhibit 8 –** David M. Herrington & Timothy D. Howard, *From Presumed Benefit to Potential Harm–Hormone Therapy and Heart Disease,* 349 NEW ENG. J. MED. 519–21 (2003).

court relied on the WHI findings in its two recent *Daubert* rulings granting defendants' challenges to plaintiffs' expert causation testimony.[21]

In July 2002, the WHI investigators reported that women taking E+P, after an average of five years on the medicine, developed invasive breast cancer at slightly higher rates than women taking placebo.[22] Expressed in relative risk terms, the increased risk of invasive breast cancer was 1.24[23]; expressed in absolute risk terms, there were 8 additional invasive cancers in every 10,000 women on E+P.[24] This risk was low – more than 97% of women who took E+P in the study did not develop breast cancer.[25] There was no statistical increase in risk of DCIS among women using E+P in the study.[26]

B. Background Regarding Plaintiff Judy Romero

Plaintiff Judy Romero began suffering from menopausal symptoms in 1996 and was prescribed Premphase by Dr. Radha Lal in December 1996.[27] Her menopausal symptoms

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[21] **Exhibit 9 –** Joint Mem. Order, *In re Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507 (Aug. 30, 2010) ("E-Only Op.") (excluding expert opinions that estrogen-alone causes breast cancer); **Exhibit 10 –** Order, *In re Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507 (Jan. 19, 2011) ("Short-Term Use Op.") (excluding expert opinions that hormone therapy use for three years or less causes breast cancer).

[22] **Exhibit 11 –** Rowan T. Chlebowski, *Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women*, 289 J. AM. MED. ASS'N 3243, 3243 (2003) ("Chlebowski 2003"); **Exhibit 12 –** FDA Approved Prempro Physician's Desk Reference Entry (Feb. 2010) ("Prempro Label") at 5.

[23] **Exhibit 11 –** Chlebowski 2003 at 3243.

[24] **Exhibit 13 –** Writing Group for the WHI Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Menopausal Women*, J. AM. MED. ASS'N at 321 (July 17, 2002) ("Writing Group 2002").

[25] *See* **Exhibit 11 –** Chlebowski 2003 at 3243. 2.3% of women taking E+P developed invasive breast cancer, compared to 1.9% of women taking placebo. *Id.* at 3250, tbl.4.

[26] *See id.* at 3248, tbl.2.

[27] **Exhibit 29 –** Oral Deposition of Judy Romero (May 22, 2009) ("Romero Dep.") at 226:10-22; **Exhibit 30 –** Oral Deposition of Radha J. Lal, M.D. (Apr. 27, 2011) at 90:9-91:15; **Exhibit 25 –** Naftalis Report at 4.

included hot flashes, inability to sleep, heart palpitations, irregular periods, and heavy bleeding.[28] In February 1998, Ms. Romero began seeing Dr. Eberhard Lotze, and he continued her prescription of Premphase.[29] Ms. Romero continued to have menopausal symptoms, despite taking HT therapy.[30] In February 2000, Dr. Lotze switched Ms. Romero from Premphase to Prempro.[31]

In March 2001, Ms. Romero was diagnosed with high grade ductal carcinoma in the left breast.[32] The tumor was removed, and she received radiation.[33] No estrogen or progesterone receptor testing was performed on her cancer, but Dr. Waldron has purportedly tested the lesion and found it to be ER+.[34] Ms. Romero took Tamoxifen for five years after the surgery and has been cancer-free since 2001.[35] Her prognosis is very good.[36]

V. ARGUMENT AND AUTHORITIES

The expert reliability standards are well-settled. This Court has "a gatekeeper obligation to 'ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable.'" *Daubert*, 509 U.S. at 589. "In the medical causation context, opinion testimony offered by an expert must be offered "with a reasonable degree of medical certainty; a hunch,

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[28] **Exhibit 29 –** Romero Dep. at 222:12-224:21.

[29] **Exhibit 31 –** Oral Deposition of Eberhard C. Lotze, M.D. (Apr. 16, 2011) ("Lotze Dep.") at 52:21-53:12, 121:4-13.

[30] *Id.* at 55:24-56:16.

[31] *Id.* at 68:11-69:16; **Exhibit 25 –** Naftalis Rep. at 5.

[32] **Exhibit 25 –** Naftalis Report at 5; **Exhibit 32 –** Oral Deposition of Karl E. Tomm, M.D. (Mar. 16, 2011) ("Tomm Dep.") at 32:4-22.

[33] **Exhibit 25 –** Naftalis Report at 6; *see also* **Exhibit 32 –** Tomm Dep. at 26:5-28:6.

[34] **Exhibit 32 –** Tomm Dep. 32:13-33:4; **Exhibit 26 –** Waldron Report at ¶ 8.

[35] **Exhibit 25 –** Naftalis Report at 6.

[36] **Exhibit 32 –** Tomm Dep. at 51:13-52:2; *see also* **Exhibit 25 –** Naftalis Report at 6 ("Ms. Romero has a Stage 0 breast cancer with a 10 year survival rate of 95%. This number was improved by her treatment to 97%."); **Exhibit 27 –** Naftalis Dep. at 99:19-22 (stating that Ms. Romero has "an excellent prognosis").

even an educated hunch, is not enough." *Warren v. Tastove*, 240 F. App'x 771, 773 (10th Cir. 2007). As the Fifth Circuit has said: "Under the regime of *Daubert*, a district judge asked to admit scientific evidence must determine whether the evidence is genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist." *Moore v. Ashland*, 151 F.3d 269, 278 (5th Cir. 1998) (en banc). Thus, even assuming an expert is qualified to render an opinion, his or her causation testimony must meet the standards of reliability set forth in *Daubert* and its progeny.

A. Differential Diagnosis Has Not Been Validated in the Medical and Scientific Communities for Determining the Cause of an Individual's Breast Cancer.

Both Dr. Naftalis and Dr. Waldron purport to have reached their conclusion that HT was the "but for" cause of Ms. Romero's DCIS of the left breast by performing a differential diagnosis.[37] The logic behind differential diagnosis – "ruling in" all plausible causes, then "ruling out" these possible causes one-by-one until only one is left – breaks down for those medical conditions where the causes are unknown to science. If, for a particular condition, the cause is unknown in a significant percentage of cases, then a doctor cannot rule out all of the causes except one, because even if all the known causes are ruled out, the unknown causes still remain. Consequently, courts have excluded causation opinions generated by "differential diagnosis" in recent cases involving asthma, autism, brain cancer, leukemia, and similar conditions for which the causes of the condition are to a great extent unknown.[38] The same is

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[37] **Exhibit 25 –** Naftalis Report at 8, 29-36, 42; **Exhibit 26 –** Waldron Report at ¶¶ 6, 11.

[38] *Hendrix v. Evenflo Co.*, 609 F.3d 1183, 1202 (11th Cir. 2010) (excluding specific-causation expert because "medical science simply does not know what causes autism," and "[o]bviously, in such a situation, the task of 'ruling out' other plausible causes is extremely complex"); *Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1343 (11th Cir. 2010) (differential diagnosis not conclusive where the cause of a disease is not understood by the medical community and excluding specific causation opinion where "neither [the expert] nor anyone else in the medical community understands the physiological process by which chondrolysis

true for breast cancer. In fact, a host of physicians across the country have testified that a differential diagnosis cannot be used to determine the cause of a woman's breast cancer because its cause is largely unknown:

- Dr. Raquel Arias (Associate Director, University of Southern California Women's & Children's Hospital): ***"[The] use of differential diagnosis to determine the cause of an individual's breast cancer is not scientifically valid or generally accepted***. . . . The cause of breast cancer cannot be determined through a process of differential diagnosis. Because we do not know the cause of breast cancer or even all of the potential risk factors, one cannot isolate the cause of an individual woman's breast cancer simply by eliminating risk factors."[39]

- Dr. Frank Ling (Chair, University of Tennessee College of Medicine, Department of Obstetrics and Gynecology): "***I have never seen [differential diagnosis] used to determine the cause of a patient's breast cancer—***as the plaintiffs' experts are attempting to do in this litigation. In order to use differential diagnosis in this manner, one would have to be able to rule out all known causes of the disease

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develops and what factors cause the process to occur" and "potentially unknown, or idiopathic alternative causes were not ruled out") (quotations omitted); *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 675 (6th Cir. 2010) (Parkinsonism); *Bland v. Verizon Wireless, L.L.C.*, 538 F.3d 893, 897 (8th Cir. 2008) ("[w]here the cause of the condition is unknown in the majority of cases, [the expert] cannot properly conclude, based upon a differential diagnosis, [the plaintiff's] exposure to freon was 'the most probable cause' of [his] exercise-induced asthma"); *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1252 (11th Cir. 2005) (simply labeling an expert's "methodology" a differential diagnosis was insufficient to prove admissibility; failing to offer a valid foundation as to how a diet supplement caused ischemic strokes and heart attacks rendered an expert's opinion unreliable); *Henrickson v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1162 (E.D. Wash. 2009) (leukemia); *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 470 (E.D. Pa. 2008) (lymphoma); *Doe v. Ortho-Clinical Diagnostics, Inc.*, 440 F. Supp. 2d 465, 478 (M.D. N.C. 2006) (excluding specific causation opinion regarding autism because the strong likelihood of unknown causes "serves to negate . . . use of the differential diagnosis technique as being proper"); *Redfoot v. B.F. Ascher & Co.*, 2007 WL 1593239, at *11 (N.D. Cal. June 1, 2007) ("[D]ifferential diagnosis is faulty because [doctor] failed to consider . . . that the cause of autism is not known today."); *Valentine v. PPG Indus., Inc.*, 821 N.E.2d 580, 599-600 (Ohio Ct. App. 2004) ("[D]ifferential diagnosis is not a reliable technique for identifying causation" of brain cancer because "medical science does not enable physicians and other scientists to pinpoint a cause of brain cancer (except for ionizing radiation). . . . [T]he present state of scientific knowledge on the cause of brain cancer precludes reliability in this context."); *Whiting v. Boston Edison Co.*, 891 F. Supp. 12, 21 n.41 (D. Mass. 1995) (leukemia).

[39] **Exhibit 14 –** Affidavit of Raquel D. Arias (Aug. 20, 2009) at ¶ 12 (emphasis added).

which is impossible to do at this point in our knowledge and understanding of breast cancer."[40]

- Dr. Kent Westbrook (Distinguished Professor of Surgery, University of Arkansas for Medical Sciences): "The method of differential diagnosis is a well accepted technique for diagnosing a particular medical condition. ***It is not generally used for the purpose of determining the cause of a specific diagnosis. The method of differential diagnosis is not usually used to attempt to determine the cause of a particular woman's breast cancer.***"[41]

- Dr. Todd Tuttle (Chief, Surgical Oncologist & Medical Director, University of Minnesota Breast Center): "I have never used differential diagnosis to determine the cause of a patient's breast cancer. ***I am not aware of any physician who has used differential diagnosis to determine the cause of a patient's cancer in clinical care***. . . . Except in this litigation, I have never heard any physician propose that the cause of a specific woman's breast cancer could be identified through differential diagnosis."[42]

- Dr. Courtney Townsend, Jr. (Distinguished Chairman, Department of Surgery, University of Texas Medical Branch—Galveston): "Over the course of my [30+ year] career, I have attended hundreds of CME seminars and reviewed many medical and scientific articles written on the subject of breast cancer . . . . I regularly engage in discussion with my colleagues on the subject of breast cancer, risk factors for breast cancer, and treatment of patients at high risk for breast cancer. ***I have never heard it suggested that anyone could determine the cause of an individual woman's breast cancer by doing a differential diagnosis or any means whatsoever.***"[43]

Medical science recognizes instead that most women diagnosed with breast cancer have ***no risk factors*** apart from simply being older.[44] If medical science cannot even point to known risk factors in most breast cancer cases, *a fortiori* it cannot identify the full range of causes. And

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[40] **Exhibit 15 –** Declaration of Frank W. Ling (Aug. 1, 2007) at ¶ 7 (emphasis added).

[41] **Exhibit 16 –** Affidavit of Kent Westbrook, M.D. (May 31, 2006) at ¶ 12 (emphasis added).

[42] **Exhibit 17 –** Affidavit of Todd M. Tuttle (Aug. 14, 2009) at ¶¶ 6, 8 (emphasis added).

[43] **Exhibit 18 –** Affidavit of Courtney M. Townsend, Jr. (Aug. 19, 2009) at ¶ 7 (emphasis added).

[44] *See* American Cancer Society, *Breast Cancer Overview*, *available at* http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-what-causes (last visited October 28, 2011) ("But risk factors don't tell us everything. Having a risk factor, or even several, doesn't mean that a woman will get breast cancer. Some women who have one or more risk factors never get the disease. And most women who do get breast cancer don't have any risk factors.").

where it cannot fill in the full spectrum of causes, it cannot reliably pinpoint the most likely cause by a process of "ruling out" causes. When a doctor has ruled out the known causes, she will still be left with the unknown causes that account for a wide band of the spectrum. *See Kilpatrick v. Breg, Inc.*, 613 F.3d 1329, 1343 (11th Cir. 2010). It is therefore not surprising that, of the almost 500 treating physicians who have been deposed in HT litigation across the country, none has testified that they use Drs. Naftalis and Waldron's methodology of differential diagnosis for determining the cause of an individual woman's breast cancer.

In this Circuit, courts have held that differential diagnosis is an accepted methodology for analyzing causation as to some diseases, but must be analyzed on a case-by-case basis for reliability.[45] A recent decision from the Texas Supreme Court confirmed that differential diagnosis can be a useful technique, particularly for treating doctors, but that the foundation of the treating physician's expert opinion must be "evaluated for reliability as carefully as any other expert's testimony." *Transcontinental Ins. Co. v. Crump*, 330 S.W.3d 211, 217 (Tex. 2010). Much turns on the specific injury at issue. In a long line of well-reasoned decisions, courts have excluded differential diagnosis-generated opinions involving diseases, like breast cancer, for which the cause(s) is unknown in a substantial proportion of cases (or where a substantial proportion of individuals suffering from the disease do not have identifiable risk factors).[46] Regarding such injuries, those courts explain, "the key foundation for applying differential diagnosis [i]s missing." *Kilpatrick*, 613 F.3d at 1343. It was exactly that reasoning that led the Sixth Circuit to uphold the exclusion of the plaintiff's expert in *Tamraz v. Lincoln Elec. Co.*, 620

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[45] *E.g.*, *Wells v. SmithKline Beecham Corp.*, No. A-06-CA-126-LY, 2009 WL 564303, at *12 (W.D. Tex. Feb. 18, 2009) (Yeakel, J.) (noting that "a differential diagnosis might provide some evidence of specific causation"). *But see Pick v. Am. Med. Sys., Inc*., 198 F.3d 241 (5th Cir. 1999) ("This circuit has not written on the question of whether an expert opinion based on differential diagnosis can meet the *Daubert* standard, and this case does not require it.").

[46] See *supra* note 38.

F.3d 665 (6th Cir. 2010). That court affirmed exclusion of testimony by the plaintiff's causation expert based on a "differential diagnosis" because "unknown (idiopathic) causation . . . currently accounts for the vast majority of Parkinson's Disease cases, making it impossible to ignore and difficult to rule out" all plausible causes of the plaintiff's injury by differential diagnosis to leave only defendants' welding rods to blame. *Id*. at 675. Failure to account for the unknown causal factors (i.e., "X"-factor(s)) of the disease at issue renders differential diagnosis "speculation, not a valid methodology." *Id*. at 674.

The *Tamraz* court's logic is irrefutable: if the cause of a disease is unknown in the majority of cases, or if all the causes of a disease are not known, then a doctor cannot pinpoint the cause in a particular case by ruling out all the causes but one. When the few known causes are ruled out, there will always remain the probability that the cause in the case at hand is one of the unknown or ideopathic causes that produce the disease in the majority of cases. Plaintiff cannot point to any analysis by any court that has allowed Dr. Naftalis to testify that explains how she can reliably rule out the X-factor as a cause of breast cancer, when the X-factor is the only explanation for breast cancer in most women.[47]

Moreover, Dr. Naftalis herself has essentially agreed that her methodology fails virtually every reliability criteria. She admitted: (1) her methodology has not been peer-reviewed, studied, tested, or validated anywhere in the world's literature or by the medical and scientific

[47] The Eighth Circuit has permitted Naftalis's testimony using a differential diagnosis to determine the cause of breast cancer. *See In re Prempro Prods. Liab. Litig.*, 586 F.3d 547, 566–67 (8th Cir. 2009). However, the analysis in that case was cursory and did not consider the line of cases cited herein that where a majority of a disease's causes are unknown, a differential diagnosis cannot be reliably employed. Moreover, the Eighth Circuit's decision did not involve a case, like here, in which so many facts regarding the Plaintiff's specific presentation were simply ignored by Dr. Naftalis and Dr. Waldron. *See* Section B, *infra*.

community for determining the cause of a woman's breast cancer;[48] (2) no other doctor, outside of litigation, has ever recorded her method of determining causation;[49] (3) she has never written in a medical record that E+P caused a patient's breast cancer, nor told a patient that her cancer would not have developed without E+P;[50] (4) she has never told a referring physician that she used her methodology to conclude that E+P caused a patient's breast cancer, nor have referring doctors ever told her that they have done so;[51] and (5) her methodology cannot be validated because she admits that there is "not a formula" for calculating the potential error rate.[52] These facts alone foreclose a finding that differential diagnosis, if used to determine the cause of an individual woman's breast cancer, satisfies the *Daubert*'s criteria for a reliable scientific methodology. *See Daubert*, 509 U.S. at 593-95, *see also Merck & Co. v. Garza*, 347 S.W.3d 256 (Tex. 2011).

B. Plaintiff's Experts Do Not Reliably Apply the Differential Diagnosis Methodology They Purport to Use.

"Ruling in" all of the scientifically plausible causes of an injury is the first step of any differential diagnosis. After considering all possible causes of an injury, the doctor then must "rule out" all causes but one. *Glastetter v. Novartis Pharm., Corp.*, 252 F.3d 986, 989 (8th Cir.

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48 **Exhibit 4 –** *Singleton* Hearing Transcript at 140:8-24; **Exhibit 19 –** Oral Deposition of Elizabeth Z. Naftalis, M.D. (July 9, 2007), *Mill v. Wyeth et al.* (Pa. Ct. Comm. Pleas) at 16:2-11; **Exhibit 20 –** Trial Transcript (Feb. 11, 2008), *Scroggin v. Wyeth et al.* (Pa. Ct. Comm. Pleas) ("*Scroggin* Trial Transcript") at 1040:12-1041:1.

49 **Exhibit 20 –** *Scroggin* Trial Transcript at 1040:8-16; **Exhibit 4 –** *Singleton* Hearing Transcript at 137:11-139:23.

50 **Exhibit 21 –** Trial Transcript (Feb. 1, 2010), *Singleton v. Wyeth* (Pa. Ct. Comm. Pleas) ("*Singleton* Trial Transcript") at 102:2–103:5; **Exhibit 20 –** *Scroggin* Trial Transcript at 1040:2-1041:1; **Exhibit 4 –** *Singleton* Hearing Transcript at 134:18-135:9.

51 **Exhibit 20 –** *Scroggin* Trial Transcript at 1040:8-11; **Exhibit 4 –** *Singleton* Hearing Transcript at 137:11-139:23.

52 **Exhibit 21 –** *Singleton* Trial Transcript at 101:14-25; *see also* **Exhibit 4 –** *Singleton* Hearing Transcript at 144:6-13; **Exhibit 22 –** Hearing Transcript (Nov. 13, 2009), *Gonzalez v. Wyeth* (Pa. Ct. Comm. Pleas), at 26:8-10.

2001). Failure to account for all scientifically plausible causes of a plaintiff's injuries renders the differential diagnosis unreliable.[53] "Simply claiming that an expert used the 'differential diagnosis' method is not some incantation that opens the *Daubert* gate." *Tamraz*, 620 F.3d at 674 (citation and quotations omitted). Here, Drs. Naftalis and Waldron failed to reliably "rule in" all of the scientifically plausible causes of Ms. Romero's breast cancer and failed to reliably "rule out" all causes but HT, and therefore their testimony should be excluded.

1. Plaintiff's Experts Did Not Reliably "Rule In" All Possible Causes of Ms. Romero's Breast Cancer.

Neither of Plaintiff's specific causation experts have "ruled in" all the plausible causes of Ms. Romero's breast cancer and for that reason alone, their methodology is flawed and unreliable. But even more importantly, Drs. Naftalis and Waldron cannot rule in HT as a potential cause of Ms. Romero's DCIS. Definitive data from the WHI clinical trial showed that there was no statistical increase in risk of DCIS among women using E+P in the study.[54] There is no dispute that the results from the WHI clinical trial are generally accepted in the medical and scientific communities. *See In re Prempro Prods. Liab. Litig.*, MDL No. 4:03-CV-1507-WRW,

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[53] *Ronwin v. Bayer Corp.*, 332 F. App'x, 508, 514 (10th Cir. 2009) (affirming a district court's decision to exclude an expert witness' causation testimony where he failed to rule out all plausible causes of the plaintiff's injury); *see also Turner v. Iowa Fire Equip. Co.*, 229 F.3d 1202, 1208 (8th Cir. 2000) (ruling expert testimony based on a differential diagnosis inadmissible where the expert "admitted that he made no attempt to consider all the possible causes, or to exclude each potential cause until only one remained, or to consider which of two or more non-excludable causes was the more likely to have caused the condition."); *Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999) (a "differential diagnosis that fails to take serious account of other potential causes may be so lacking that it cannot provide a reliable basis for an opinion on causation."); *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 179 (6th Cir. 2009) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 760 (3d Cir. 1994)) (a reliable differential diagnosis must rule out alternative causes by "'standard diagnostic techniques [on] which doctors'" normally rely.).

[54] **Exhibit 11 –** Chlebowski 2003 at 3248, tbl. 2; *see also* **Exhibit 27 –** Naftalis Dep. at 91:19-24 ("Q. Is it not true that the Women's Health Initiative writing group reported no increased risk of DCIS in women taking E plus P? . . . A. Once again, I'd have to look at that, but I believe that's true.").

2010 WL 3447293, at *5 (E.D. Ark. Aug. 30, 2010) (characterizing the results of the WHI clinical trial as "reliable and generally accepted"). Plaintiff does not have scientifically reliable evidence that women taking HT have an increased risk of developing DCIS. Accordingly, Drs. Naftalis and Waldron cannot reliably testify that HT caused Ms. Romero's DCIS, and therefore their testimony should be excluded.

2. Plaintiff's Experts Did Not Properly Rule Out Alternative Causes of Ms. Romero's Breast Cancer.

Critical to a specific causation analysis is that Plaintiff's experts must "rule out" other plausible causes of Ms. Romero's breast cancer, as required both by the expert reliability standards and any properly conducted differential diagnosis. *See Glastetter*, 252 F.3d at 989. "If other possible causes of an injury cannot be ruled out, or at least the probability of their contribution to causation minimized, then the 'more likely than not' threshold for proving causation may not be met."[55] As the Texas Supreme Court recently explained, "when the facts support several possible conclusions, only some of which establish that the defendant's negligence caused the plaintiff's injury, the expert must explain to the fact finder why those conclusions are superior based on verifiable medical evidence, not simply the expert's opinion." *Jelinek v. Casas*, 328 S.W.3d 526, 536 (Tex. 2010). Drs. Naftalis and Waldron's differential diagnosis fails to meet this standard.

First, Dr. Naftalis failed to rule out Ms. Romero's endogenous estrogen the cause of her breast cancer. The starting premise of Dr. Naftalis's methodology – that Ms. Romero was "hormone deficient" and therefore lacked sufficient endogenous estrogen to develop ER+ cancer in the absence of HT – lacks support in the factual record. Dr. Naftalis conceded that she has no

[55] FEDERAL JUDICIAL CENTER, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 470 n.112 (2d ed. 2000) (quoting *Cavallo v. Star Enter.*, 892 F. Supp. 756, 771 (E.D. Va. 1995)).

measurements of Ms. Romero's endogenous estrogen before she began HT therapy.[56] Her premise is based solely on the fact that Ms. Romero had menopausal symptoms when she began HT in 1996. But she had no explanation for why Ms. Romero's menopausal symptoms continued while she was on E+P medications. And both doctors agree that tumors similar to Ms. Romero's frequently occur in women who have never taken E+P.[57] Indeed, 70% of the diagnosed breast cancers in post-menopausal women who experience hot flashes are ER-PR-positive carcinomas, yet the women have never used HT.[58]

Second, Drs. Naftalis and Waldron failed to reliably rule out Ms. Romero's risk factors for developing cancer. Dr. Naftalis and Dr. Waldron collectively identified a number of Ms. Romero's risk factors – her age, breast density, family history, failure to breastfeed, and oral contraceptive use – but summarily dismissed each without any meaningful analysis or explanation for why and how each risk factor was ruled out.[59] Dr. Naftalis and Dr. Waldron acknowledged that Ms. Romero had dense breasts, but they did not articulate how breast density was excluded as a possible cause.[60] In fact, Dr. Naftalis admitted that breast density can increase an individual's risk of breast cancer 400-600 percent.[61] Dr. Naftalis also ignored the fact that unknown causes – "X" factors – play a role in most breast cancers in the United States. Most women that develop breast cancer have no known risk factors other than being female and of

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56 **Exhibit 27 –** Naftalis Dep. at 56:12-19.

57 **Exhibit 23 –** Oral Deposition of Elizabeth Z. Naftalis (Nov. 4, 2011), *Ashlock v. Wyeth et al.* ("Naftalis *Ashlock* Dep.") at 17:10-19; **Exhibit 28 –** Waldron Dep. at 63:17-64:1.

58 **Exhibit 23 –** Naftalis *Ashlock* Dep. at 18:12-20:22.

59 **Exhibit 25 –** Naftalis Report at 30-36; **Exhibit 26 –** Waldron Report at ¶ 11.

60 **Exhibit 25 –** Naftalis Report at 34; **Exhibit 27 –** Naftalis Dep. at 48:12-25; **Exhibit 28 –** Waldron Dep. at 66:11-24.

61 **Exhibit 27 –** Naftalis Dep. at 34:15-24; *see also* **Exhibit 24 –** Boyd, N. et al., *Heritability of Mammographic Density, A Risk Factor for Breast Cancer*, 347 NEW ENG. J. MED. 886, 886-894 (2002).

advancing age.[62] And Dr. Waldron does not make any attempt whatsoever to rule out any other possible cause. Consequently, the opinions of both of these experts should be excluded under *Daubert*.

VI. CONCLUSION

For the foregoing reasons, this Court should grant Wyeth's motion and exclude the testimony and expert reports of Dr. Naftalis and Dr. Waldron in their entirety.

Dated: February 24, 2012

Respectfully Submitted,

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[62] *See supra* note 45.

CERTIFICATE OF CONFERENCE

Counsel has complied with the meet and confer requirement in Local Rule CV-7(h). This motion is opposed. On February 17th and 20th, counsel for Plaintiff, Bryan Aylstock, and counsel for Defendant, Janelle L. Davis, conducted the conferences required by this rule. Despite a good faith effort by both sides, an agreement could not be reached and the discussions have conclusively ended in an impasse, leaving an open issue for the court to resolve.

/s/ Janelle L. Davis
Janelle L. Davis

CERTIFICATE OF SERVICE

I hereby certify that on this 24th day of February, 2012 a true and correct copy of the foregoing was filed with the Court and served via electronic notification on all counsel of record.

/s/ Janelle L. Davis
Janelle L. Davis

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